IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicants:	Hissink, et al.	Examiner:	Jeffrey T. Palenik
Serial No.:	10/521,126	Art Unit:	1615
Confirm. No.:	6484	Docket:	294-207 PCT/US/RCE
Filed:	January 12, 2005		
For:	BIODEGRADABLE PHASE SEPARATED SEGMENTED MULTI BLOCK CO-POLYMERS		

Mail Stop Amendment
Commissioner for Patents
P.O. Box 1450
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DECLARATION UNDER 37 C.F.R. 1.132 OF
THEODORUS ADRIANUS CORNELIS FLIPSEN

Sir:

I, Theodorus Adrianus Cornelius Flipsen, hereby declare and state as follows:

1.   I am one of the inventors named in the above captioned patent application.

2.   Beginning in 2004, I have worked for InnoCore Technologies for more than five (5) years and conducted research and development relating to biodegradable multi-block copolymers. In my current position, I am the responsible manager in the Biomaterials Research and Development Group. I have extensive knowledge relating to processes for manufacturing

block copolymers and structure-property relationships. I have a Masters degree in Polymer

chemistry & physics from The University of Groningen in Groningen, The Netherlands and a

Doctorate in Polymer chemistry and physics from the same university. Since 1990, I have

worked in the field of biodegradable polymers. Furthermore, I am a named inventor or co-

inventor of various novel polymer systems and polymer applications that have resulted in 8

unique patent families.

3.   I have read the March 31, 2009 Office Action in the above-captioned patent

application and I am familiar with the references cited by the Examiner, i.e., the article titled,

"*Macromolecular Chemistry and Physics*," by Penco et al. ("Penco") and U.S. Patent

Application Publication No. US 2001/0009662 by Cohn et al. ("Cohn").

4.   The present invention teaches randomly segmented multiblock copolymers (for

example, ABBBABAAABBAAAA... etc.), which means that blocks A and B are randomly (or

statistically) distributed over the block copolymer. This is only possible by using an additional

molecule that links the blocks A and B randomly together, the so-called chain-extender (or chain

linker). Only by using a chain extender molecule allows A and B to be present in different,

adjustable ratios (see also section 6).

5.   If there is a certain preference for a certain block due to reactivity or preferred

presence at the reactive ends of a growing chain in the reaction mixture such influences will

result in a more pronounced segmented distribution over the chain (e.g.,

AAAAAABBBBBBBBAAAAAAARBBBBAAAAAABBBBBBBB... etc.). Again, the use of a chain extension molecule allows these types of block copolymers to be formed.

6.   Furthermore, the approach of the current invention allows blocks A and B (as well as C or D, etc.) to be built into the multiblock copolymer in various ratios. This provides greater control of (and also more pronounced) phase separation and the physical and chemical properties of the block copolymers. The current invention can be used to, for instance, form phase separating block copolymers with A:B ratios of 90:10 (which means that the segments A form the continuous phase and segments B form a phase that is distributed therein). The current invention can also be used to, for instance, form phase separating block copolymers with ratios of 10:90 (which means that the segments B form the continuous phase and segments A form a phase that is distributed therein).

7.   I note that the Examiner erroneously identifies PEG as a chain-extender (see Office Action, page 5, second full paragraph). As clearly follows from pending claims 4 and 9, PEG can be used as or in a pre-polymer segment, but it is not used as a chain-extender.

8.   In contrast to the present invention, Penco teaches alternating multiblock copolymers (ABABABAB... etc.). In the method taught by Penco, A segments and B segments are always present in a 50:50 (mole) ratio. A and B have to react with each other for chain growth, there is no separate chain extender molecule or reactant present. Phase separation may be possible, but there is only very limited control of it. Also, the control of and influence on properties is limited by segment compositions and the length of the segment.

9.   Although the abstract and the introduction of Penco mention a chain extension

reaction, this involves functionalizing one block (e.g., A) so that it will react with another block

(e.g., B). This interpretation is supported by Scheme 1 of Penco, which shows that the polymer

chain is built up by a reaction of two macromers. A third reactant for connecting the two

macromers is not used. As explained above, this is fundamentally different from the present

invention, which uses a separate chain-extender molecule that connects the A and B blocks. This

is also the classical definition of a chain extender.

10.   Although the Examiner argues that various PLGA compositions could be taken

for the A block and combined to the reactive B blocks to provide a multiblock copolymer with

random A segments, such a copolymer is neither taught nor suggested by Penco. Moreover,

although such a copolymer may have different A segments, it would still have an alternating

configuration with respect to block B (e.g., $A^1BA^2BA^1BA^3B$... etc.). This is fundamentally

different from the claims, which require a random distribution of both segments A and B.

11.   The random distribution of the A and B segments in the claims not only implies

that different A segments can be used but, in particular, it implies that the distribution of the

segments is random. In contrast, the copolymer taught by Penco has segments A and B that are

distributed in alternating form.

12.   In accordance with the present invention, a chain-extender Q is used, which

results in multiblock copolymers having structures such as ...A—Q—A—Q—B—Q—B—Q—

B—Q—A—Q—B—Q—... In the method taught by Penco, a chain-extender Q is not present.

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The method of our invention uses relatively low molecular weight A and B blocks and, as a result, the amount of Q in the final multiblock copolymer is substantial and affects the properties of the block copolymers that are formed.

13.   Cohn describes the preparation of very specific block copolymers having the structure BA—Q—AB. The polymers do not contain reactive end groups for further reaction. These structures cannot be used to form randomly (statistically) segmented multi-block copolymers, let alone block copolymers that can have a wide range of ratios of the A and B blocks.

14.   Cohn further teaches the preparation of copolymers with the structure —ACA—Q—ACA—Q—ACA—Q— etc. Again, this does not result in a randomly segmented multi-block copolymer. Cohn does not teach or suggest using A and C multi-functional prepolymers that are chain extended with Q in a statistical, random manner.

15.   The polymers of Cohn are always controlled in their alternation. Also, the ratio between A and B, or A and C is fixed. Phase separation may be possible, but similar to the teachings of Penco, there is only very limited control of and influence on the phase separation. Also, the control of and influence on properties is limited by segment compositions and the length of the segments.

16.   Also with respect to Cohn, the Examiner argues that the skilled person could have used chemically distinct polyester "A" blocks. However, similar to the structures taught by

Penco, this would yield a copolymer having an alternating configuration with respect to block

C (e.g., $A^1CA^2CA^1CA^3C$... etc.). In addition, the claims require both segments A and C to be

randomly distributed, which cause the distribution of the segments to be random. In contrast, the

copolymers of Cohn have segments A and C that are distributed in alternating form. For the sake

of clarity, it is not argued here that Cohn teaches that block A or C can be different in

composition. Instead, Cohn is distinguishable because in a single multi-block copolymer block

A of whatever composition or length is always followed by block C of whatever composition or

length. In the current invention, this type of multi-block copolymers is not claimed. Also, the

current invention claims compositions where A:B or A:C are present in any ratio. In the case of

Cohn (as well as Penco) A:B is always 50/50 for AB block copolymers or 66/33 for ACA block

copolymers.

17.   The present invention allows the preparation of unique molecular architectures

that are not obvious in view of a combination of the teachings of Penco and Cohn. There is no

teaching or suggestion in Penco and Cohn, either alone or in combination, of randomly

segmented multiblock copolymers, wherein the distinct blocks may be present in all ratios, as

required by the claims of the present application.

18.   I disagree with the Examiner's finding on page 9 of the Office Action, in the third

paragraph of the section titled, "Response to Arguments," which states that:

> Penco et al. further teaches on page 1740 (*Molecular Characteristics*), that the
> PLGA-PCDT block copolymer samples had different compositions of the PLGA
> blocks as well as different lengths of the PCDT blocks. Thus, since the PLGA
> oligomers may differ in their composition (e.g. mole ratio of LA/GA), it follows

that Penco, suggests that different polymers of PLGA can reside within the same
PLGA-PCDT copolymer.

On the basis of this sentence, the Examiner seems to conclude that Penco teaches a block

copolymer having a random distribution of the segments. This conclusion is, however, incorrect

for the reasons discussed below.

19.   The paragraph on page 1740 of Penco that was cited by the Examiner states that:

Tab. 1 shows the results obtained by means of conventional SEC and by off-line
viscosimetry for a commercial sample of PLGA (LA/GA = 75/25 mole ratio) and
for six samples of PLGA-PCDT block copolymers. The PLGA-PCDT block
copolymer samples had different composition of the PLGA blocks and different
length of the PCDT blocks.

20.   The Examiner bases his finding that "Penco suggests that different polymers of

PLGA can reside within the same PLGA-PCDT copolymer" on the premise that "since the

PLGA oligomers may differ in their composition (e.g. mole ratio of LA/GA)." The paragraph on

page 1740 of Penco discloses different PLGA-PCDT copolymers in which different polymers of

PLGA reside in the different copolymers. However, Penco does not teach or suggest that

"different polymers of PLGA can reside within the same PLGA-PCDT copolymer." There is no

teaching or suggestion in Penco that any of the PLGA-PCDT copolymers includes more than one

type of PLGA polymer. This is illustrated in Table 1, wherein six different PLGA-PCDT

copolymers are characterised and each of the six includes only one type of PLGA polymer.

21.   Although there are different lengths of PCDT blocks in different copolymers

(PCDT530, PCDT1250, and PCDT2000), each block copolymer has only one length of PCDT

block. Penco does not disclose a single copolymer in which, for example, a PCDT530 block and a PCDT1250 block are present in the same PLGA-PCDT copolymer. The same applies to the PLGA block compositions in Table 1. Although different PLGA block compositions occur in different copolymers (molar ratio between D,L-lactic acid and glycolic acid can be 50/50 or 75/25), each PLGA-PCDT copolymer has only one composition of the PLGA block. Penco does not disclose a single copolymer in which, for example, a PLGA block composition with a molar ratio between D,L-lactic acid and glycolic acid of 50/50 and a PLGA block composition with a molar ratio of 75/25 are present in the same PLGA-PCDT copolymer.

22.   Even if one of ordinary skill in the art would draw the same conclusions as the Examiner from Penco (which I explicitly dispute), the present invention would still differ from the teaching in Penco. If Penco used different "A" blocks (i.e., different PLGA block compositions) and different "B" blocks (i.e., different PCDT block lengths), the block copolymers of Penco that would come closest to the invention would have alternating A blocks and B blocks and be represented by a formula similar to: ...$A^3B^1A^2B^3A^2B^3A^1B^1$... However, these copolymers are not the same as the block copolymers of the invention, because the block copolymers in the claims require a random distribution of the segments. In contrast, the A and B segments in Penco's block copolymers are distributed in a regular fashion, namely in an alternating manner. The fact the A-blocks may differ in LA/GA ratio and the B-blocks may differ in length does not result in multi-block copolymers that would give a true random distribution of A- and B-blocks. Penco does not teach or suggest block copolymers that have

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multiple A segments next to each other and/or multiple B segments next to each other e.g.,

.......$A^3A^2A^3B^1B^2A^1B^5B^4B^1A^1A^2A^1$.......

23.   Also, there are very few reasons for choosing different PLGA compositions or different PCDT block lengths in one multi-block copolymer. The effect on properties (in this case including, in particular phase separation) is very limited or nil. Accordingly, one skilled in the art would not find it obvious to use different PLGA compositions or different PCDT block lengths in one multi-block copolymer.

24.   I base my finding that Penco teaches block copolymers with alternating A blocks and B blocks on the reaction disclosed by Penco in Scheme 1 on page 1740. Penco et al. made multi-block copolymers through reacting a block A (PLGA), which block having an OH group on one end and a carboxylic group on the other end (HO-A-COOH) with a block B (PCDT), which block having on both ends a chloroformate group. It is commonly known to one of ordinary skill in the art that chloroformates react very effectively with protonic groups such as OH and COOH groups. That is the reason why Penco et al. modified the PCDT OH end groups to chloroformates, as they wanted to effectively connect the PCDT blocks to the PLGA blocks forming an AB multi-block copolymer. Those skilled in the art would know that a reaction of a composition containing only HO-A-COOH or ClC(=O)O-B-O(O=)CCl will not take place under the reaction conditions shown in Scheme 1 on page 1740. Perhaps under other conditions a reaction may take place, but never effectively and in those conditions no multi-block copolymer

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will be formed. Of course, such other conditions are also not described or suggested by Penco et al.

25.   In order to be complete, Penco et al. clearly talk about chain extending oligomeric PLGA with oligomeric α,ω-bis(chloroformates) deriving from hydroxyl-terminated PCDT (e.g. page 1744, Conclusions). What they actually mean is that the PLGA and PCDT oligomers react with each other to form a chain extended AB multi block copolymer (where A = PLGA and B = PCDT or vice versa). The block copolymer is thus based on A and B alternating: ....ABABABAB....

26.   It is important to understand that a polymer or pre-polymer (even if low in molecular weight) always has a Gaussian distribution of chain lengths. One can normally not speak about a single molecular weight, but only about a molecular weight distribution. In the context of the current invention, each block is considered to have a normal molecular weight distribution. Each block of distinct length is not considered to be different from a block of another distinct length. A pre-polymer having a distribution in molecular weight or even having various molecular weight distributions is considered to be one distinct block in the multi-block copolymer in the current invention.
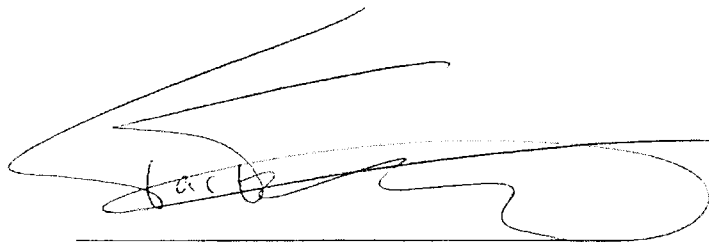
27.   The Examiner mentions that Penco suggests a non-uniform block distribution (page 1742, left column). Firstly, non-uniform block distribution would not be possible given the synthetic route. Secondly, Penco et al. do not teach or suggest making multi-block copolymers with non-uniform block distribution. Thirdly, Penco et al. try to find an explanation (hypothesis)

for the fact that a single AB multi-block copolymer showed a deviation in its molecular weight

determination. This single multi-block copolymer was the PLGA50/50-PCDT1250 composition.

All the other compositions followed a trend; the PLGA50/50-PCDT1250 composition did not. It

is most likely that a measurement was not conducted properly, rather than the block distribution

caused the observation of a deviation in the molecular weight determination.

28.   The Examiner indicates in his comments that the instant claims are directed to a

biodegradable copolymer composition, rather than the production of such a composition. This is

true. However, the composition of the copolymers is inextricably determined by the preparation

route.

29.   I hereby declare that all statements made herein are of my own knowledge and are

true, and that all statements made on information and belief are believed to be true; and further

that the statements have been made with the knowledge that willful false statements and the like

so made are punishable by fine or imprisonment, or both, under § 1001 of Title 18 of the United

States Code and that such willful false statements may jeopardize the validity of any patent

issuing on the present invention.

Dated: August 2 8 , 2009

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Theodorus Adrianus Cornelius Flipsen

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